REMARKS

1. Request For Reexamination

Applicant appreciates the Examiner's acknowledgement of the timely filing of a Request for Continued Examination under 37 C.F.R. 1.114 and her withdrawal of the finality of the previous Office Action.

2. Change in Patent Examiners

Applicant acknowledges that the patent examiner has changed to Ms. Carla Myers.

3. Status of the Claims

Currently, claims 18-31 and 33 are pending. Claims 30-31 and 33 were previously withdrawn by the Applicant without prejudice or disclaimer of the subject matter therein. Claims 32 and 34 have been cancelled without prejudice or disclaimer of the subject matter therein. Claims 18-29 are currently pending. Claim 18 has been amended without prejudice or disclaimer of the subject matter thereof. Applicant acknowledges that the Examiner has deemed claims 30-31 and 33 withdrawn as drawn to a nonelected invention. Applicant has included complete text of all such withdrawn claims as a courtesy to the Examiner. Applicant appreciates the Examiner's acknowledgement of its timely traversal of the restriction requirement filed on February 16, 2007.

4. Status of Rejections of Record

Applicant appreciates the Examiner's acknowledgement that the previous rejections of the claims under 35 U.S.C. 102 and 103 were obviated by the amendments to the claims.

5. Amendments

Applicant has herein provided a complete amended claim set with all claims properly identified per 37 C.F.R. 1.121 and the full text of withdrawn claims 30-31 and 33.

6. Rejection of Claims 18-29 under 35 U.S.C. 112, first paragraph

The Examiner has rejected claims 18-29 under 35 U.S.C. 112, first paragraph for the reasons of record. Specifically, the Examiner does not feel the specification as originally filed provides support for the amendment to the claims to recite "mixing non-equal amounts of said sample and said standard."

Applicant respectfully asserts there is support in the specification for non-equal amounts of DNA as it relates to the difference in the amount of standard bound to a microparticle compared with the amount of sample bound to a microparticle. The presence of a difference in the amount of standard versus sample binding to microparticles is indicative of aneuploidy. With that said, solely for the sake of advancing prosecution, and without prejudice or disclaimer of the subject matter therein, claim 18 has been amended to remove the term, "non-equal amounts of said sample and said standard" and has replaced it with the phrase, "mixing said fluorescently-labeled polynucleotide sample and said non-aneuploid-flourescently-labeled polynucleotide standard" to assist in clarifying this aspect of the present invention.

In light of the foregoing, Applicant respectfully requests withdrawal of the rejection of claims 18-29 under 35 U.S.C. 112, first paragraph.

7. Rejection of claims 18-29 under 35 U.S.C. 112, second paragraph

The Examiner has rejected claims 18-29 under 35 U.S.C. 112, second paragraph for the reasons of record. Specifically the Examiner feels it is unclear as to how one would detect aneuploidy in one or more chromosomes of a subject simultaneously because it is unclear as to what is encompassed by simultaneously detecting aneuploidy in one chromosome. With that said, solely for the sake of advancing prosecution, and without prejudice or disclaimer of the subject matter therein, claim 18 has been amended to state that the assay is for detection of aneuploidy in a subject, rather than aneuploidy in one or more chromosomes of a subject in order to assist in clarifying this aspect of the present invention.

In light of the foregoing, Applicant respectfully requests withdrawal of the rejection of claims 18-29 of under 35 U.S.C. 112, first paragraph.

8. Double Patenting Rejection

The Examiner has rejected claims 18-29 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of copending Application No. 11/631,714 in view of Singh et al (WO 02/40698). Applicant will address this issue by filing a terminal disclaimer, should the need arise.

9. Rejection of claims 18-21, 23, 24 and 26-28 under 35 U.S.C. 103(a)

The Examiner has rejected claims 18-21, 23-24 and 26-28 under 35 U.S.C. 103(a) as being unpatentable over Pinkel (U.S. Patent No. 6,562,565)("Pinkel") in view of Mohammed (PGPUB 2003/0124584) ("Mohammed") and further in view of Singh et al. (WO 02/40698) ("Singh") for the reasons of record.

Initially, Applicant would like to point out that in order for an Examiner to establish a prima facie case of obviousness, the Examiner must show that each and every one of the claim limitations was suggested or taught by the prior art being relied upon. *In re Royka,* 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson,* 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). When an independent claim is deemed nonobvious under 35 USC 103, then all claims depending therefrom are nonobvious as well. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed Cir. 1988).

Applicant respectfully submits that the Examiner has not overcome this burden. Specifically, instant claim 18 contains a limitation directed to the detection of aneuploidy in a subject. In contrast, the Pinkel reference cited by the Examiner discloses copy number detection in genomes, such as deletions, duplications, inversions and translocations of segments of DNA as copy number variations are often indicative of particular disease states. The present invention is quite different from the methods of Pinkel in that it is directed to detection of aneuploidy, which is indicative of deletions or duplications of entire chromosomes, rather than merely segments of DNA along one or more chromosomes. Additionally, it is important to note that copy number variations are not indicative of chromosomal number and variations can occur without change in the chromosomal number of a subject.

Further, as previously stated, Pinkel teaches away from the assays of the present invention. The methods of the present invention deduce the copy number of the chromosome of interest based on a ratio of the signal from the control DNA and the signal from the subject DNA when each are present in equal amounts and the binding agent is limiting. The specification states, "[t]he method of the present invention is based on the competitive binding, to a limited amount of complementary binding agent, of equal amounts of DNA from a sample and standard of the same organism." (Paragraph 0131, line 1 to 5)

Applicant again respectfully asserts that Pinkel never mentions competitive binding and the conclusions in this reference are in no way based on the results of a competitive binding assay. In fact, Pinkel's method would fail if it did not have an excess of immobilized binding agent because if the binding sites were saturated, or nearly saturated, under one set of conditions, the method would not be able to detect an increase in copy number as no more target would bind and no more signal would be detected. Pinkel also discloses a concern over the assay principles of linearity and dynamic range and states, "[t]he sensitivity, linearity and dynamic range achievable from the various combinations of fluorochrome and membranes can thus be determined." (Pinkel column 8, lines 48-51). In short, Pinkel does not at all describe a competitive binding assay, let alone an interpretation of the results of such an assay.

Pinkel, as also previously discussed, describes that comparing binding of reference probes to target elements with the binding of test probe to target elements can detect variations in copy number from normal (due to binding differences)." (col 2 lines 66 through col 3, line 27) As stated above, the Applicant's method does not use reference probes. The Applicants' method also does not attempt to measure binding of reference probes to target elements nor compare the binding of reference probes to the binding of target elements in any way.

As such, Applicant respectfully contends that the Pinkel reference discloses a method that not only detects entirely different end-points (copy number of particular segments of DNA versus chromosome number) but is also technically distinct from the present invention. Applicant respectfully asserts the aforementioned deficiencies are not taught or suggested by Mohammed or Singh. Thus, Applicant respectfully submits that the prior art references do not teach or suggest all the limitations of the claims.

Furthermore, to establish a *prima facie* case of obviousness under 35 U.S.C. 103(a), the Examiner must show that the proposed modification or combination of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209 (Fed. Cir. 1991). In *Amgen*, the Court explained that while the idea may have been "obvious to try," many pitfalls existed that would have eliminated a reasonable expectation of success.

Applicant asserts the Examiner has not met this burden. In the instant case, one of ordinary skill in the art would have no reasonable expectation of success in combining Pinkel with Mohammed et al to achieve the teachings of the instant invention. As Applicant has previously stated, Pinkel does not teach the presence of non-equal binding of the sample and the standard to the binding agent (microparticle). Moreover, Pinkel does not teach the use of size, number or fluorescence for multiplexing nor does it teach the use of multiple internal controls for fluorescence level testing. Also, Applicant asserts the teachings of Pinkel require equal amounts of test and samples whereas in the present invention, this is not necessary.

Further, Applicant respectfully asserts the aforementioned deficiencies are not taught or suggested by Mohammed et al or by Singh. The Examiner has cited Mohammed for the principal of taking equitable amounts of genomic DNA from test and reference samples, differentially labeling the samples with fluorescent dyes and co-hybridizing them to BACS that contain the cloned genomic DNA fragments that cover the entirety of the cell's genome. Co-hybridization then produces a fluorescently-labeled array. The Examiner has cited Singh to argue that it discloses a multiplex assay that can be used to simultaneously analyze different target nucleic acids. In applying *Amgen* to the instant case, due to the many pitfalls that exist, one of ordinary skill in the art would not have a reasonable expectation of success in combining the co-hybridization methods of Mohammed with Pinkel and further combining that with the multiplex assay of Singh to achieve the instant invention. Applicant submits that none of the aforementioned pitfalls can reasonably be expected to be overcome by the addition of utilizing the combination of co-hybridization to produce fluorescently-labeled arrays with microparticles of different sizes labeled with different fluorophores of different emission intensities.

Furthermore, to establish a *prima facie* case of obviousness under 35 U.S.C. 103(a), the Examiner must show that the prior art relied upon contains some suggestion that would have

motivated the skilled artisan to modify a reference or to combine references. *Karsten Mfg. Corp. v. Cleveland Gulf Co.,* 242 F.3d 1376 (Fed. Cir. 2001). In light of the foregoing paragraph and analysis, there would be no motivation to combine the teachings Singh with that of Pinkel and Mohammed. As previously stated, one of ordinary skill would have no expectation of success in combining Pinkel and Mohammed due to the many pitfalls and thus no motivation to further combine the teaching of Singh related to multiplex assays since they do not overcome any of the aforementioned pitfalls.

In light of the above arguments, Applicant respectfully requests withdrawal of the rejections of record of claims 18-21, 23-24 and 26-28 under 35 U.S.C. 103(a).

10. Rejection of Claim 22 under 35 U.S.C. 103(a)

The Examiner has rejected claim 22 under 35 U.S.C. 103(a) as being unpatentable over Pinkel (U.S. Patent No. 6,562,565) ("Pinkel") in view of Mohammed (PGPUB 2003/0124584) ("Mohammed") and Singh et al. (WO 02/40698) ("Singh") and further in view of Ibanez et al. (Mol. Reprod. Dev. 2001 Feb; 58(2): 166-72) ("Ibanez") for the reasons of record.

As previously asserted by Applicant, in order for an Examiner to establish a *prima facie* case of obviousness, the Examiner must show that each and every one of the claim limitations was suggested or taught by the prior art being relied upon. *In re Royka,* 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Additionally, "[a]ll words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson,* 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

Applicant respectfully submits that this burden has not been met. The present invention discloses the creation of a detectable signal due to non-equal binding of the sample and the standard to microparticles. As Applicant has previously pointed out in its response to the rejections above, there are many aspects of the present invention that Pinkel does not teach.

As discussed above, Applicant asserts the aforementioned deficiencies were not taught or suggested by Mohammed or Singh even in view of Ibanez. The Examiner states, "Ibanez teaches a method of detecting genetic mosaicism and teaches application of this method to the analysis of transgenic cattle and sheep founder animals." In now way does this overcome the

deficiencies of Pinkel, Mohammed or Singh. Thus, Applicant respectfully submits that the prior art references do not teach or suggest all the limitations of the claims.

In light of the above argument, Applicant respectfully requests withdrawal of the rejections of record of claim 22 under 35 U.S.C. 103(a).

11. Rejection of Claim 25 under 35 U.S.C. 103(a)

The Examiner has rejected claim 25 under 35 U.S.C. 103(a) as being unpatentable over Pinkel in view of Mohammed and Singh and further in view of Gvakharia et al. (Fertility and Sterility, 2002 Sept; 78 (Supplement 1):S229) ("Gvakharia").

As previously asserted by Applicant, in order for an Examiner to establish a *prima facie* case of obviousness, the Examiner must show that each and every one of the claim limitations was suggested or taught by the prior art being relied upon. *In re Royka,* 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Additionally, "[a]ll words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson,* 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

Applicant respectfully submits that this burden has not been met. The present invention discloses the creation of a detectable signal due to non-equal binding of the sample and the standard to microparticles. As Applicant has previously pointed out in its response to the rejections above, there are many aspects of the present invention that Pinkel does not teach.

As discussed above, Applicant asserts the aforementioned deficiencies were not taught or suggested by Mohammed or Singh even in view of Gvakharia. The Examiner states, "Gvakaria teaches collecting cells from the blastomere stage to perform preimplantation genetic diagnosis." In now way does this overcome the deficiencies of Pinkel, Mohammed or Singh. Thus, Applicant respectfully submits that the prior art references do not teach or suggest all the limitations of the claims.

In light of the above argument, Applicant respectfully requests withdrawal of the rejections of record of claim 22 under 35 U.S.C. 103(a).

12. Rejection of Claim 29 under 35 U.S.C. 103(a)

The Examiner has rejected claim 29 under 35 U.S.C. 103(a) as being unpatentable over Pinkel in view of Mohammed and Singh and further in view of Bitner et al. (U.S. Patent No: 6,787,307) ("Bitner").

As repetitively asserted by Applicant, in order for an Examiner to establish a *prima facie* case of obviousness, the Examiner must show that each and every one of the claim limitations was suggested or taught by the prior art being relied upon. *In re Royka,* 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Additionally, "[a]ll words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson,* 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

Applicant respectfully submits that this burden has not been met. As previously mentioned, the present invention discloses the creation of a detectable signal due to non-equal binding of the sample and the standard to microparticles. As Applicant has previously pointed out in its response to the rejections above, there are many aspects of the present invention that Pinkel does not teach.

As discussed above, Applicant asserts the aforementioned deficiencies were not taught or suggested by Mohammed or Singh even in view of Bitner The Examiner states, "Bitner teaches a method of detecting nucleic acid sequences in a sample using silica microparticles that are silanized and coupled to nucleic acids." In no way does this overcome the deficiencies of Pinkel, Mohammed or Singh. Thus, Applicant respectfully submits that the prior art references do not teach or suggest all the limitations of the claims.

In light of the above argument, Applicant respectfully requests withdrawal of the rejections of record of claim 29 under 35 U.S.C. 103(a).

Concluding Remarks

In view of the foregoing, Applicant respectfully submits that the rejections have been overcome and respectfully requests that the rejections be removed and the claims placed in condition for allowance. In the event the Examiner has any questions regarding the Applicant's position, a telephone call to the undersigned representative is requested.

Respectfully Submitted,

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Date

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